Pharmacological Treatment of Mixed States

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ABSTRACT:

We systematically reviewed published pharmacological treatment data for "mixed states/episodes" in mood disorders including "with mixed features" in DSM-5. We searched: PUBMED, MEDLINE, COCHRANE LIBRARY, clinicaltrials.gov, current-trials.com (key words: "mixed states/features" AND "bipolar" AND "depressive symptoms/bipolar depression" AND "manic symptoms" AND "treatment" AND "DSM-5") to April 2016. We applied a quality of evidence approach (first-degree evidence: randomised placebo controlled studies of pharmacological interventions used in monotherapy; second-degree evidence comprised a similar design in the absence of a placebo group or of combination therapy; third degree evidence comprised case reports, case series, post-hoc analysis of primary data, non-controlled cohort studies and reviews of published studies).

We found very little primary double-blind, placebo-controlled studies of the treatment of mixed states: the preponderance of available data derives from sub-group analysis performed on studies that originally involved manic patients.

Introduction

Mixed states present particular challenges to the treating clinician and even the prevalence rate changes significantly among studies and in relation to diagnostic criteria used. In DSM-IV, a diagnosis of a mixed episode required simultaneously all criteria for a manic or a major depressive episode. In clinical practice individuals infrequently meet these full criteria. After a 14-year development process including approximately 400 people from different professions and 39 countries, DSM-5 appeared in May 2013. The new DSM-5 "specifier" adopts a broader approach towards mixed states. In the case of depressive episodes, there is a requirement for the presence of at least three manic/hypomanic symptoms (including elevated mood, inflated self-esteem, decreased need for sleep and an increase in energy or goal-directed activities), occurring nearly every day during the most recent two weeks of the major depressive episode, notably overlap with symptoms of major depression is restricted. In the case of mania or hypomania, the specifier requires the presence of at least three symptoms of depression (including depressed mood, diminished interest or pleasure, slowed physical and emotional reaction, fatigue or loss of energy, and recurrent thoughts of death) together with the episode of mania/hypomania, nearly every day throughout the most recent week of a manic episode or during the most recent four days of a hypomanic episode.

Mixed states are generally held to be less responsive to pharmacological treatment and response to mood stabilizers and other pharmacotherapies is poor[1,2]. Antidepressants are generally avoided because of exacerbation of manic symptoms and a feared increased risk of suicidality which is already high[3]. However, the use of an atypical antipsychotic-antimanic agent in some bipolar disorder patients may decrease suicidal ideation[4]. As a result, the choice of medication is usually based on individual factors and short/long-term harms, safety and tolerability parameters. The aim of this review is to review the pharmacological treatment of "mixed states/episodes" as defined by DSM-IV and DSM-5 manic episodes "with mixed features" .

Methods

Searches

PUBMED, MEDLINE, and the Cochrane library were searched from January 1980 to April 2016 for all publications regarding treatment of mixed features as defined by DSM-IV and DSM-5 manic episodes "with mixed features". Clinical trials registries, 'clinicaltrials.gov' and 'controlled-trials.com', were scrutinised for trials. Search terms included: "Mixed states OR Mixed features" AND "Bipolar disorder'' AND "depressive symptoms OR bipolar depression" AND "Manic symptoms'' AND "Treatment'' AND ''DSM-5''. Related publications were hand searched from the reference lists of every identified primary study.

Study selection

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[5] guidelines. Articles were screened and selected for full-text review if they met our selection criteria. Once identified titles and abstracts were reviewed independently by two the authors (AC,, AY) and discrepancies were resolved by consensus among all the authors.

Quality assessment

First-degree studies included double blind, placebo controlled randomised controlled trials (RCTs) of pharmacological interventions used in monotherapy. Second-degree referred to a similar design without placebo group +/- combination therapy and third degree referred to any other type of published studies.

Results

The searches identified 913 studies of which 73 met inclusion criteria and investigated mixed states in bipolar disorder. Non-original studies (including editorials, book reviews and letters to the editor) and studies without full-text available were excluded.

These studies evaluated antipsychotics (n=39), mood stabilizers (n=14) and combination therapies (n=20) in patients with DSM-IV mixed episodes or DSM-5 mixed features. Pharmacological evidence for each class of medication is described below and organised according to clinical presentation, length of treatment and degree of evidence (Supplementary Tables with details available upon request).

Antipsychotic medication with mood stabilising properties

1) OLANZAPINE

Acute treatment studies (≤ 8 weeks)

We identified two first degree studies comparing olanzapine with placebo [6,7], one second degree evidence study comparing olanzapine with haloperidol[8] and two with risperidone[9,10].

Longer term (≥ 8 weeks), maintenance and relapse prevention studies

We identified six second degree studies. One open label post-hoc analysis compared olanzapine with placebo and further five trials compared olanzapine with haloperidol (6-week continuation phase), sodium valproate, lithium and asenapine in two reports (see below for asenapine). A post hoc-analysis open label study of a randomized, placebo-controlled trial[11] compared olanzapine with placebo in mixed episode patients for 6-12-week [12]. A subsequent 6-week continuation phase of Tohen et al. 12-week comparison trial was also identified (olanzapine vs haloperidol)[10]. Tohen and

others[13] analyzed the efficacy of olanzapine vs. valproate in the treatment of mania and mixed episodes. A further study of 52 weeks[14] compared the efficacy of olanzapine and lithium monotherapy in relapse/recurrence prevention of mood episodes among remitted patients previously treated with a combination therapy of these two compounds (for 6-12 weeks).

2) QUETIAPINE

Acute treatment (≤ 8 weeks)

We identified five first degree acute phase studies. Three studies compared quetiapine with placebo [15-17] and two compared quetiapine with lithium or paroxetine and placebo[18,19]. Another randomized controlled study compared quetiapine with paliperidone extended release to placebo (see paliperidone). A second degree evidence continuation phase of the study which compared quetiapine with paliperidone without placebo is descibed below (see paliperidone)[20].

Longer term (≥ 8 weeks), maintenance and relapse prevention studies

One maintenance study compared quetiapine with lithium and placebo as open label extension of a randomised controlled trial in Bipolar I disorder for up to 104 weeks [21]..

3) ARIPIPRAZOLE

Acute treatment (≤ 8 weeks)

We identified five first degree evidence acute phase trials with aripiprazole. Four studies compared aripiprazole with placebo [22-25] and one with lithium and placebo [26]. A one second degree evidence comparison trial analyzed the efficacy of aripiprazole vs. haloperidol[27].

Longer term (≥ 8 weeks), maintenance and relapse prevention studies

We identified one first degree long term trial which compared aripiprazole with placebo [28] and two second degree extension studies[26,27] comparing aripiprazole with lithium and haloperidol respectively (the treatment received in the first 3 week of treatment are discussed above).

4) ASENAPINE

Acute treatment (≤ 8 weeks)

There are two first degree evidence trials[29,30] assessing asenapine in the managment of mixed affective symptoms compared with olanzapine and placebo. McIntyre and others combined the above described studies[29,30] in a post-hoc analysis[31] based on the DSM-5 mixed specifier for the diagnosis of manic episodes.

Longer term (≥ 8 weeks), maintenance and relapse prevention studies

We reported two second degree evidence trials regarding long term treatment of asenapine compared with olanzapine by McIntyre and others. The authors designed these two stepped progressive studies originating from the first 3 week trial by randomising the placebo group into active treatment[32,33].

5) LURASIDONE

Acute treatment (≤ 8 weeks)

We found evidence of efficacy in acute bipolar depression, supported by two monotherapy randomized clinical trials[34,35] and one second degree adjunctive therapy study (see combination therapy)[36].

Longer term (≥ 8 weeks), maintenance and relapse prevention studies

No studies were identified.

6) ZIPRASIDONE

Acute treatment (≤ 8-weeks)

We identified one first degree evidence trial assessing efficacy of ziprasidone compared with placebo in major depressive episodes with 2 or 3 concomitant manic symptoms[37]. A second degree study is available from a pooled analysis[38] of mixed patient with dysphoric mania previously enrolled in two similar placebo controlled trials[39,40].

Longer term (≥ 8 weeks), maintenance and relapse prevention studies

No studies were identified.

7) RISPERIDONE

Acute treatment (≤ 8-weeks)

We identifyed one firts degree trial[41] comparing risperidone to placebo in mixed affective conditions.

Longer term (≥ 8 weeks), maintenance and relapse prevention studies

No studies were available.

8) PALIPERIDONE

Acute treatment (≤8-weeks)

We indentified two first degree trials[20,42] assessing efficacy of paliperidone in mixed affective conditions.

Longer term (≥ 8 weeks), maintenance and relapse prevention studies

Vieta et al. performed a randomized, placebo- active-controlled study of paliperidone extended release for the treatment of acute manic and mixed Bipolar I disorder [20]..

9) CLOZAPINE

Acute and maintenance treatment

In a case series by Suppes and others 85 consecutive patients were treated with clozapine. Seven subjects had treatment-resistant bipolar disorder and manic episodes associated with significant depressive symptoms. All patients displayed significant reductions in affective and psychotic symptoms when treated with clozapine alone or in combination with lithium, an antidepressant, or sodium valproate. Clozapine effects were often evident within the first few weeks of treatment and sustained over the 3-5 years follow-up period[43].

10) CARIPRAZINE

Acute treatment (≤ 8-weeks)

The three identified first degree randomized controlled trials measured the effect of cariprazine on manic and depressive symptoms in acute mania or mixed episodes [44-46].

Longer term (≥ 8 weeks), maintenance and relapse prevention studies

Longer-term treatment of subjects with Bipolar I illness was investigated in an open, 16-week study that followed up 402 patients[47,48].

Ongoing trials

An ongoing international 8-week study[49] of cariprazine vs. placebo in bipolar depression registrated on the ClinicalTrials.gov website is currently investigating subjects with Bipolar I depression with a verified previous manic or mixed episode, without psychotic features, aged 18–65 , total HAMD score of ≥20, HAMD Item 1 score of ≥2, and CGI-S of ≥4 to be randomized to cariprazine 0.75, 1.5, or 3.0 mg/day, or placebo.

Mood stabilizers in managment of mixed affective features

1) DIVALPROEX

Acute treatment (≤ 8 weeks)

We found four first degree Divalproex vs. placebo acute treatment trials[50-53].

Maintenance treatment (≥ 8 weeks) No maintenance or relapse prevention trials with divalproex monotherapy were found. Comparison studies are analized in the section below (see lithium).

2) LITHIUM

Acute treatment (≤ 16 weeks)

We identifyed two second degree comparison trials with divalproex (in manic/mixed bipolar patients) [54] or lamotrigine[55] in bipolar depression.

Maintenance/relapse prevention treatment (≥ 16 weeks)

Only one trial was identified comparing lithium monotherapy vs. placebo as a prophylactic intervention in major unipolar depression and hypomania in bipolar disorder[56]. Three long-term

phase trials compared lithium with divalproex and placebo[57] and two lithium with lamotrigine and placebo (described with lamotrigine below).

3) CARBAMAZEPINE

Acute treatment (≤ 8 weeks)

Weisler and others[58] reported a post hoc analysis of two randomised controlled studies[59,60]. The first trial showed higher response rates in mixed or manic patients treated with carbamazepine-extended release (CBZ-ER) vs. placebo (42% vs. 22% rispectively). The second trial reported response rates in acute manic patient treated with CBZ-ER vs. placebo in the range of 60.8% and 28.7% respectively for mixed patients suggesting that carbamazepine might be effective to treat both manic and depressive symptoms.

Maintenance treatment (≥ 8 weeks)

Ketter and colleagues[61], in an additional secondary analysis confirmed that also long-term monotherapy with extended-release is efficacious against Bipolar I disorder mixed and manic episodes.

4) LAMOTRIGINE

Acute treatment (≤ 16 week)

We found only one first degree study of Bipolar I disorder experiencing a major depressive episode treated with lamotrigine (50 or 200 mg/day) or placebo in monotherapy for a 7-week period. [62]

Maintenance/ relapse prevention (≥ 16 weeks)

Two first degree trials compared lamotrigine with lithium[63,64].

5) GABAPENTIN

Only one open label study investigated gabapentin as adjunctive treatment for treatment resistant Bipolar mixed states presenting at both poles of the illness[65].

COMBINATION THERAPY

1) ARIPIPRAZOLE PLUS MOOD STABIZERS

Acute treatment (≥ 8 weeks)

One trial investigated aripiprazole adjuvant to other mood stabilizers (lithium or valproate) in the treatment of acute phase mixed states[66].

Longer term maintenance or relapse prevention (≥ 8 weeks)

Two first degree trials[67,68] compared aripiprazole adjunct to a stabilizers (lithium/valproate and lamotrigine) vs. placebo. A further second degree extension trial compared aripiprazole with lthium or valproate without the placebo arm[69].

2) OLANZPINE PLUS MOOD STABILIZERS

Acute treatment (≤ 8 weeks)

Three first degree trials compared olanazapine with a mood stabilizer (lithium or valproate) vs. placebo [70-72].

Longer term maintenance/relapse prevention (≥ 8 weeks)

Tohen et al. followed up patients who achieved syndromic remission for 18 months in a double-blind trial [73], derived from the 6 weeks trial discussed above [71] .

3) OLANZPINE – FLUOXETINE COMBINATION (OFC)

Acute treatment (≤ 8 weeks)

One first degree study[74] compared olanzapine monotherapy and in combination (OFC) vs. placebo which included a post-hoc mixed depressed patients analysis. Two second degree trials were also available assessing OFC vs. lamotrigine in bipolar depression with fixed [75] and flexible doses [76].

Longer term maintenance and relapse prevention (≥ 8 weeks)

Brown and others also conducted a 6-month long-term follow-up trial[77] of the 7-week study above[76] and reported greater response of OFC flexible doses in comparison with lamotrigine (titrated up to 200 mg/day) for both depressive and manic symptoms in Bipolar depression.

4) QUETIAPINE PLUS MOOD STABILIZERS

Acute treatment (≤ 8 weeks)

Suppes and others assessed adjunctive quetiapine treatment in Bipolar II patients experiencing hypomania with mixed symptoms in a two-site, randomized, placebo-controlled, double-blind, 8-week investigation [78].

Longer term maintenance/relapse prevention (≥ 8 weeks)

Two placebo-controlled trials[79,80] evaluated maintenance treatment with quetiapine (compared to placebo) as an adjunct to lithium or divalproex.

5) RISPERIDONE PLUS MOOD STABILIZERS

Acute treatment (≤ 8 weeks)

No studies were found.

Longer term manitenzance/relapse prevention (≥ 8 weeks)

Woo and others investigated the efficacy of risperidone in combination with mood stabilizers in a 24-week, open-label third-degree combination trial [81].

6) LURASIDONE PLUS MOOD STABILIZERS

Acute treatment (≤ 8 weeks)

Loebel and others investigated the efficacy of lurasidone as adjunctive therapy with lithium or valproate for the treatment of Bipolar I depression in a 6-week, randomized, placebo-controlled trial [36].

Longer term maintenance/relapse prevention

No trials available for review.

7) ZIPRASIDONE PLUS MOOD STABILIZERS

Acute treatment (≤ 8 weeks)

No trials available for review.

Longer term maintenance/relapse prevention (≥ 8 weeks)

Bowden and colleagues assessed the maintenance efficacy of ziprasidone compared to placebo as an adjunct to a mood stabilizer in manic/mixed bipolar I patients for up to 6 months (after ≥ 8 consecutive weeks of stability with open-label ziprasidone and lithium or valproate)[82].

8) LAMOTRIGINE PLUS MOOD STABILIZERS

Acute treatment (≤ 8 weeks)

Van der Loos and colleagues[83] added lamotrigine or placebo to the ongoing lithium treatment of patients with bipolar depression.

Longer term maintenance/relapse prevention (≥ 8 weeks)

Bowden and others trialled lamotrigine alone or in combination with divalproex-extended release in recently depressed patients with bipolar disorder in a maintenance study after 8-week open stabilization phase with lamotrigine or divalproex[84].

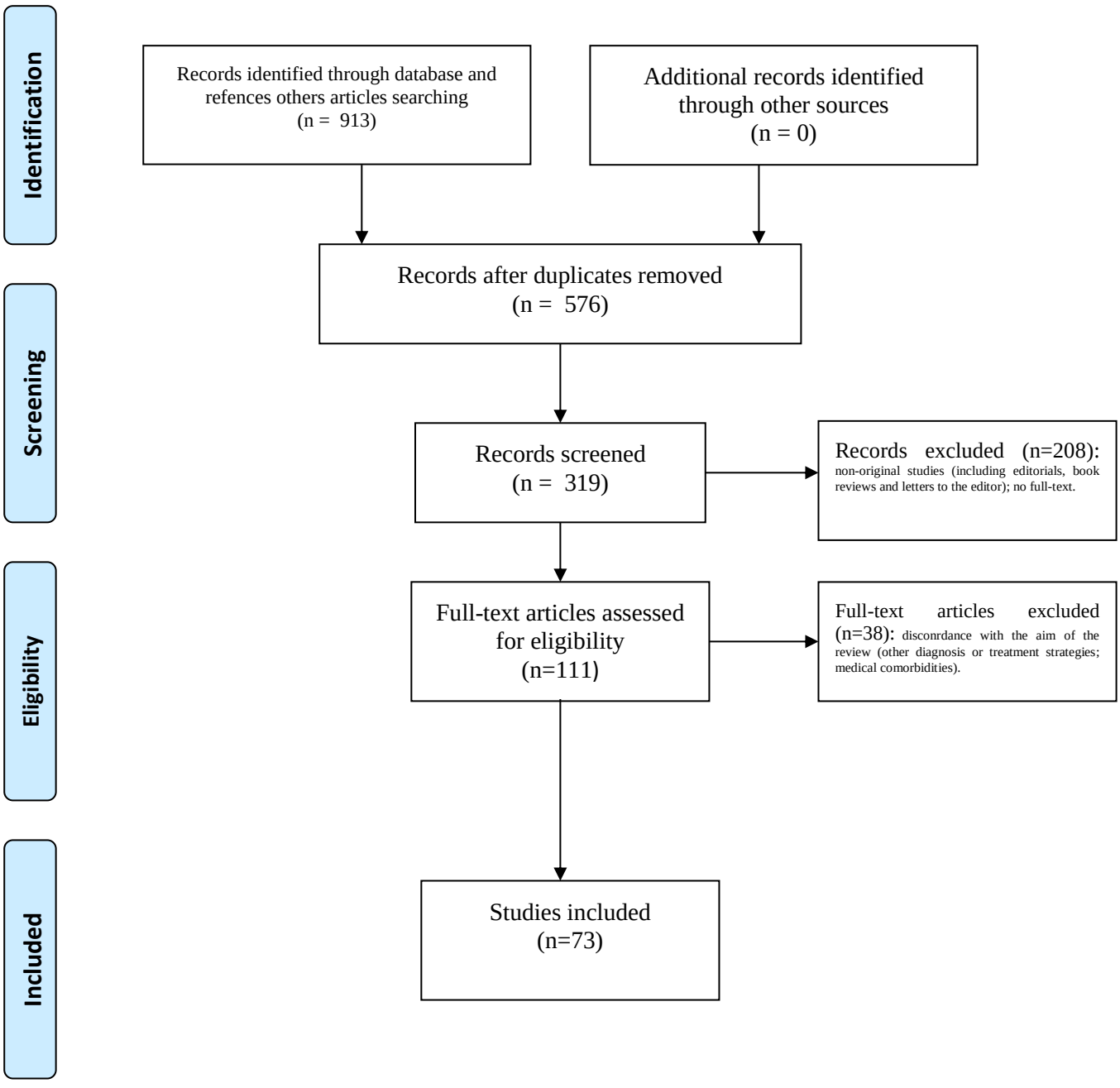
Discussion

We found that the vast majority of published RCTs initially recruited both pure manic and mixed patients as defined in the DSM-IV classification system and that additional sub-analyses were performed to identify effects in a subgroup of mixed patients. A major shortfall in the literature is that mixed depressive cases are not usually reported in depression RCTs. This subgroup approach has several shortcomings: first, the resulting sample sizes are usually small and thus "negative" trials could have been underpowered to detect existing differences between groups or "positive" trials might have an increased probability of being falsely positive; second, mixed patients enrolled in RCTs are probably less severely ill than those seen in clinical practice, and thirdly, the categorical definition of DSM-IV limits the number of patients thus identified, since it requires the co-occurrence of a full manic and a full depressive episode. Additional limitations of our work must be acknowledged. Although our search strategy was comprehensive and included several search terms, there is still the chance that we have missed relevant papers or studies. This review did not include books, or clinical trials that have looked at the effects of other, non-pharmacological, treatment modalities such as psychosocial interventions or ECT. We report results distinguishing between manic and depressive outcomes when available, which may be more in line with the clinical need to know to what extent the chosen medication is able to resolve both manic and depressive symptoms in mixed states and bipolar depression or, conversely, to independently treat one or the other. Moreover, this is in line with the new "with mixed features" categorization of mood episodes in DSM-5, as the distinction in efficacy based on the polarity of concomitant

symptoms may be closer to the real clinical setting. The currently available evidence does not meet meet clinicians' demands. Therefore, there is a clear need to conduct well-powered trials specifically designed to enrol the full range of mixed features.

References, tables and figures.

PRISMA Flow Diagram



1. Swann AC, Lafer B, Perugi G, et al. Bipolar mixed states: an international society for bipolar disorders task force report of symptom structure, course of illness, and diagnosis. *The American journal of psychiatry* 2013; **170**(1): 31-42.
2. Vieta E, Valenti M. Mixed states in DSM-5: implications for clinical care, education, and research. *Journal of affective disorders* 2013; **148**(1): 28-36.
3. Castle DJ. Bipolar mixed states: still mixed up? *Current opinion in psychiatry* 2014; **27**(1): 38-42.
4. Houston JP, Ahl J, Meyers AL, Kaiser CJ, Tohen M, Baldessarini RJ. Reduced suicidal ideation in bipolar I disorder mixed-episode patients in a placebo-controlled trial of olanzapine combined with lithium or divalproex. *The Journal of clinical psychiatry* 2006; **67**(8): 1246-52.
5. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Annals of internal medicine* 2009; **151**(4): W65-94.
6. Tohen M, Sanger TM, McElroy SL, et al. Olanzapine versus placebo in the treatment of acute mania. Olanzapine HGEH Study Group. *The American journal of psychiatry* 1999; **156**(5): 702-9.
7. Tohen M, Jacobs TG, Grundy SL, et al. Efficacy of olanzapine in acute bipolar mania: a double-blind, placebo-controlled study. The Olanzipine HGGW Study Group. *Archives of general psychiatry* 2000; **57**(9): 841-9.
8. Novick D, Reed C, Haro JM, et al. Comparison of olanzapine and risperidone in the EMBLEM Study: translation of randomized controlled trial findings into clinical practice. *International clinical psychopharmacology* 2010; **25**(5): 257-63.
9. Perlis RH, Baker RW, Zarate CA, Jr., et al. Olanzapine versus risperidone in the treatment of manic or mixed States in bipolar I disorder: a randomized, double-blind trial. *The Journal of clinical psychiatry* 2006; **67**(11): 1747-53.
10. Tohen M, Goldberg JF, Gonzalez-Pinto Arrillaga AM, et al. A 12-week, double-blind comparison of olanzapine vs haloperidol in the treatment of acute mania. *Archives of general psychiatry* 2003; **60**(12): 1218-26.
11. Tohen M, Calabrese JR, Sachs GS, et al. Randomized, placebo-controlled trial of olanzapine as maintenance therapy in patients with bipolar I disorder responding to acute treatment with olanzapine. *The American journal of psychiatry* 2006; **163**(2): 247-56.
12. Tohen M, Sutton VK, Calabrese JR, Sachs GS, Bowden CL. Maintenance of response following stabilization of mixed index episodes with olanzapine monotherapy in a randomized, double-blind, placebo-controlled study of bipolar 1 disorder. *Journal of affective disorders* 2009; **116**(1-2): 43-50.
13. Tohen M, Ketter TA, Zarate CA, et al. Olanzapine versus divalproex sodium for the treatment of acute mania and maintenance of remission: a 47-week study. *The American journal of psychiatry* 2003; **160**(7): 1263-71.
14. Tohen M, Greil W, Calabrese JR, et al. Olanzapine versus lithium in the maintenance treatment of bipolar disorder: a 12-month, randomized, double-blind, controlled clinical trial. *The American journal of psychiatry* 2005; **162**(7): 1281-90.
15. Young AH, McElroy SL, Bauer M, et al. A double-blind, placebo-controlled study of quetiapine and lithium monotherapy in adults in the acute phase of bipolar depression (EMBOLDEN I). *The Journal of clinical psychiatry* 2010; **71**(2): 150-62.
16. McElroy SL, Weisler RH, Chang W, et al. A double-blind, placebo-controlled study of quetiapine and paroxetine as monotherapy in adults with bipolar depression (EMBOLDEN II). *The Journal of clinical psychiatry* 2010; **71**(2): 163-74.

17. Calabrese JR, Keck PE, Jr., Macfadden W, et al. A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. *The American journal of psychiatry* 2005; **162**(7): 1351-60.
18. Thase ME, Macfadden W, Weisler RH, et al. Efficacy of quetiapine monotherapy in bipolar I and II depression: a double-blind, placebo-controlled study (the BOLDER II study). *Journal of clinical psychopharmacology* 2006; **26**(6): 600-9.
19. Suppes T, Datto C, Minkwitz M, Nordenhem A, Walker C, Darko D. Effectiveness of the extended release formulation of quetiapine as monotherapy for the treatment of acute bipolar depression. *Journal of affective disorders* 2010; **121**(1-2): 106-15.
20. Vieta E, Nuamah IF, Lim P, et al. A randomized, placebo- and active-controlled study of paliperidone extended release for the treatment of acute manic and mixed episodes of bipolar I disorder. *Bipolar disorders* 2010; **12**(3): 230-43.
21. Weisler RH, Nolen WA, Neijber A, Hellqvist A, Paulsson B. Continuation of quetiapine versus switching to placebo or lithium for maintenance treatment of bipolar I disorder (Trial 144: a randomized controlled study). *The Journal of clinical psychiatry* 2011; **72**(11): 1452-64.
22. Keck PE, Jr., Marcus R, Tourkodimitris S, et al. A placebo-controlled, double-blind study of the efficacy and safety of aripiprazole in patients with acute bipolar mania. *The American journal of psychiatry* 2003; **160**(9): 1651-8.
23. Sachs G, Sanchez R, Marcus R, et al. Aripiprazole in the treatment of acute manic or mixed episodes in patients with bipolar I disorder: a 3-week placebo-controlled study. *Journal of psychopharmacology (Oxford, England)* 2006; **20**(4): 536-46.
24. Suppes T, Eudicone J, McQuade R, Pikalov A, 3rd, Carlson B. Efficacy and safety of aripiprazole in subpopulations with acute manic or mixed episodes of bipolar I disorder. *Journal of affective disorders* 2008; **107**(1-3): 145-54.
25. Findling RL, Nyilas M, Forbes RA, et al. Acute treatment of pediatric bipolar I disorder, manic or mixed episode, with aripiprazole: a randomized, double-blind, placebo-controlled study. *The Journal of clinical psychiatry* 2009; **70**(10): 1441-51.
26. Keck PE, Orsulak PJ, Cutler AJ, et al. Aripiprazole monotherapy in the treatment of acute bipolar I mania: a randomized, double-blind, placebo- and lithium-controlled study. *Journal of affective disorders* 2009; **112**(1-3): 36-49.
27. Vieta E, Bourin M, Sanchez R, et al. Effectiveness of aripiprazole v. haloperidol in acute bipolar mania: double-blind, randomised, comparative 12-week trial. *The British journal of psychiatry : the journal of mental science* 2005; **187**: 235-42.
28. Keck PE, Jr., Calabrese JR, McIntyre RS, et al. Aripiprazole monotherapy for maintenance therapy in bipolar I disorder: a 100-week, double-blind study versus placebo. *The Journal of clinical psychiatry* 2007; **68**(10): 1480-91.
29. McIntyre RS, Cohen M, Zhao J, Alphs L, Macek TA, Panagides J. A 3-week, randomized, placebo-controlled trial of asenapine in the treatment of acute mania in bipolar mania and mixed states. *Bipolar disorders* 2009; **11**(7): 673-86.
30. McIntyre RS, Cohen M, Zhao J, Alphs L, Macek TA, Panagides J. Asenapine in the treatment of acute mania in bipolar I disorder: a randomized, double-blind, placebo-controlled trial. *Journal of affective disorders* 2010; **122**(1-2): 27-38.
31. McIntyre RS, Tohen M, Berk M, Zhao J, Weiller E. DSM-5 mixed specifier for manic episodes: evaluating the effect of depressive features on severity and treatment outcome using asenapine clinical trial data. *Journal of affective disorders* 2013; **150**(2): 378-83.
32. McIntyre RS, Cohen M, Zhao J, Alphs L, Macek TA, Panagides J. Asenapine versus olanzapine in acute mania: a double-blind extension study. *Bipolar disorders* 2009; **11**(8): 815-26.

33. McIntyre RS, Cohen M, Zhao J, Alphs L, Macek TA, Panagides J. Asenapine for long-term treatment of bipolar disorder: a double-blind 40-week extension study. *Journal of affective disorders* 2010; **126**(3): 358-65.
34. Loebel A, Cucchiaro J, Silva R, et al. Lurasidone monotherapy in the treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study. *The American journal of psychiatry* 2014; **171**(2): 160-8.
35. Suppes T, Silva R, Cucchiaro J, et al. Lurasidone for the Treatment of Major Depressive Disorder With Mixed Features: A Randomized, Double-Blind, Placebo-Controlled Study. *The American journal of psychiatry* 2015: appiajp201515060770.
36. Loebel A, Cucchiaro J, Silva R, et al. Lurasidone as adjunctive therapy with lithium or valproate for the treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study. *The American journal of psychiatry* 2014; **171**(2): 169-77.
37. Patkar A, Gilmer W, Pae CU, et al. A 6 week randomized double-blind placebo-controlled trial of ziprasidone for the acute depressive mixed state. *PloS one* 2012; **7**(4): e34757.
38. Stahl S, Lombardo I, Loebel A, Mandel FS. Efficacy of ziprasidone in dysphoric mania: pooled analysis of two double-blind studies. *Journal of affective disorders* 2010; **122**(1-2): 39-45.
39. Keck PE, Jr., Versiani M, Potkin S, West SA, Giller E, Ice K. Ziprasidone in the treatment of acute bipolar mania: a three-week, placebo-controlled, double-blind, randomized trial. *The American journal of psychiatry* 2003; **160**(4): 741-8.
40. Potkin SG, Keck PE, Jr., Segal S, Ice K, English P. Ziprasidone in acute bipolar mania: a 21-day randomized, double-blind, placebo-controlled replication trial. *Journal of clinical psychopharmacology* 2005; **25**(4): 301-10.
41. Khanna S, Vieta E, Lyons B, Grossman F, Eerdekens M, Kramer M. Risperidone in the treatment of acute mania: double-blind, placebo-controlled study. *The British journal of psychiatry : the journal of mental science* 2005; **187**: 229-34.
42. Berwaerts J, Xu H, Nuamah I, Lim P, Hough D. Evaluation of the efficacy and safety of paliperidone extended-release in the treatment of acute mania: a randomized, double-blind, dose-response study. *Journal of affective disorders* 2012; **136**(1-2): e51-60.
43. Suppes T, McElroy SL, Gilbert J, Dessain EC, Cole JO. Clozapine in the treatment of dysphoric mania. *Biological psychiatry* 1992; **32**(3): 270-80.
44. Durgam S, Starace A, Li D, et al. The efficacy and tolerability of cariprazine in acute mania associated with bipolar I disorder: a phase II trial. *Bipolar disorders* 2015; **17**(1): 63-75.
45. Sachs GS, Greenberg WM, Starace A, et al. Cariprazine in the treatment of acute mania in bipolar I disorder: a double-blind, placebo-controlled, phase III trial. *Journal of affective disorders* 2015; **174**: 296-302.
46. Calabrese JR, Keck PE, Jr., Starace A, et al. Efficacy and safety of low- and high-dose cariprazine in acute and mixed mania associated with bipolar I disorder: a double-blind, placebo-controlled study. *The Journal of clinical psychiatry* 2015; **76**(3): 284-92.
47. Ketter TA. phase III, open-label, 16-week study of flexibly dosed cariprazine in 402 patients with bipolar I disorder. Presented at: 53rd Annual Meeting of the New Clinical Drug Evaluation Unit; May 28-31, 2013; Hollywood, FL.; 2013.
48. Long-term safety and tolerability of cariprazine for bipolar I disorder. Forest Laboratories ICgwAahcgcsNAN.
49. Safety t, and efficacy of cariprazine for patients with bipolar depression. Forest Laboratories, Inc. ClinicalTrials.gov website. Available at: http://clinicaltrials.gov/ct2/show/NCT01396447. Accessed November 6 2012.

50. Bowden CL, Swann AC, Calabrese JR, et al. A randomized, placebo-controlled, multicenter study of divalproex sodium extended release in the treatment of acute mania. *The Journal of clinical psychiatry* 2006; **67**(10): 1501-10.
51. Davis LL, Bartolucci A, Petty F. Divalproex in the treatment of bipolar depression: a placebo-controlled study. *Journal of affective disorders* 2005; **85**(3): 259-66.
52. Muzina DJ, Gao K, Kemp DE, et al. Acute efficacy of divalproex sodium versus placebo in mood stabilizer-naive bipolar I or II depression: a double-blind, randomized, placebo-controlled trial. *The Journal of clinical psychiatry* 2011; **72**(6): 813-9.
53. Ghaemi SN, Gilmer WS, Goldberg JF, et al. Divalproex in the treatment of acute bipolar depression: a preliminary double-blind, randomized, placebo-controlled pilot study. *The Journal of clinical psychiatry* 2007; **68**(12): 1840-4.
54. Freeman TW, Clothier JL, Pazzaglia P, Lesem MD, Swann AC. A double-blind comparison of valproate and lithium in the treatment of acute mania. *The American journal of psychiatry* 1992; **149**(1): 108-11.
55. Suppes T, Marangell LB, Bernstein IH, et al. A single blind comparison of lithium and lamotrigine for the treatment of bipolar II depression. *Journal of affective disorders* 2008; **111**(2-3): 334-43.
56. Dunner DL, Stallone F, Fieve RR. Lithium carbonate and affective disorders. V: A double-blind study of prophylaxis of depression in bipolar illness. *Archives of general psychiatry* 1976; **33**(1): 117-20.
57. Bowden CL, Collins MA, McElroy SL, et al. Relationship of mania symptomatology to maintenance treatment response with divalproex, lithium, or placebo. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology* 2005; **30**(10): 1932-9.
58. Weisler RH, Hirschfeld R, Cutler AJ, et al. Extended-release carbamazepine capsules as monotherapy in bipolar disorder : pooled results from two randomised, double-blind, placebo-controlled trials. *CNS drugs* 2006; **20**(3): 219-31.
59. Weisler RH, Kalali AH, Ketter TA. A multicenter, randomized, double-blind, placebo-controlled trial of extended-release carbamazepine capsules as monotherapy for bipolar disorder patients with manic or mixed episodes. *The Journal of clinical psychiatry* 2004; **65**(4): 478-84.
60. Weisler RH, Keck PE, Jr., Swann AC, Cutler AJ, Ketter TA, Kalali AH. Extended-release carbamazepine capsules as monotherapy for acute mania in bipolar disorder: a multicenter, randomized, double-blind, placebo-controlled trial. *The Journal of clinical psychiatry* 2005; **66**(3): 323-30.
61. Ketter TA, Kalali AH, Weisler RH. A 6-month, multicenter, open-label evaluation of beaded, extended-release carbamazepine capsule monotherapy in bipolar disorder patients with manic or mixed episodes. *The Journal of clinical psychiatry* 2004; **65**(5): 668-73.
62. Calabrese JR, Bowden CL, Sachs GS, Ascher JA, Monaghan E, Rudd GD. A double-blind placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression. Lamictal 602 Study Group. *The Journal of clinical psychiatry* 1999; **60**(2): 79-88.
63. Bowden CL, Calabrese JR, Sachs G, et al. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently manic or hypomanic patients with bipolar I disorder. *Archives of general psychiatry* 2003; **60**(4): 392-400.
64. Calabrese JR, Bowden CL, Sachs G, et al. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder. *The Journal of clinical psychiatry* 2003; **64**(9): 1013-24.

65. Perugi G, Toni C, Ruffolo G, Sartini S, Simonini E, Akiskal H. Clinical experience using adjunctive gabapentin in treatment-resistant bipolar mixed states. *Pharmacopsychiatry* 1999; **32**(4): 136-41.
66. Vieta E, T'Joen C, McQuade RD, et al. Efficacy of adjunctive aripiprazole to either valproate or lithium in bipolar mania patients partially nonresponsive to valproate/lithium monotherapy: a placebo-controlled study. *The American journal of psychiatry* 2008; **165**(10): 1316-25.
67. Marcus R, Khan A, Rollin L, et al. Efficacy of aripiprazole adjunctive to lithium or valproate in the long-term treatment of patients with bipolar I disorder with an inadequate response to lithium or valproate monotherapy: a multicenter, double-blind, randomized study. *Bipolar disorders* 2011; **13**(2): 133-44.
68. Carlson BX, Ketter TA, Sun W, et al. Aripiprazole in combination with lamotrigine for the long-term treatment of patients with bipolar I disorder (manic or mixed): a randomized, multicenter, double-blind study (CN138-392). *Bipolar disorders* 2012; **14**(1): 41-53.
69. Vieta E, Owen R, Baudelet C, McQuade RD, Sanchez R, Marcus RN. Assessment of safety, tolerability and effectiveness of adjunctive aripiprazole to lithium/valproate in bipolar mania: a 46-week, open-label extension following a 6-week double-blind study. *Current medical research and opinion* 2010; **26**(6): 1485-96.
70. Houston JP, Tohen M, Degenhardt EK, Jamal HH, Liu LL, Ketter TA. Olanzapine-divalproex combination versus divalproex monotherapy in the treatment of bipolar mixed episodes: a double-blind, placebo-controlled study. *The Journal of clinical psychiatry* 2009; **70**(11): 1540-7.
71. Tohen M, Chengappa KN, Suppes T, et al. Efficacy of olanzapine in combination with valproate or lithium in the treatment of mania in patients partially nonresponsive to valproate or lithium monotherapy. *Archives of general psychiatry* 2002; **59**(1): 62-9.
72. Baker RW, Brown E, Akiskal HS, et al. Efficacy of olanzapine combined with valproate or lithium in the treatment of dysphoric mania. *The British journal of psychiatry : the journal of mental science* 2004; **185**: 472-8.
73. Tohen M, Chengappa KN, Suppes T, et al. Relapse prevention in bipolar I disorder: 18-month comparison of olanzapine plus mood stabiliser v. mood stabiliser alone. *The British journal of psychiatry : the journal of mental science* 2004; **184**: 337-45.
74. Tohen M, Vieta E, Calabrese J, et al. Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. *Archives of general psychiatry* 2003; **60**(11): 1079-88.
75. Benazzi F, Berk M, Frye MA, Wang W, Barraco A, Tohen M. Olanzapine/fluoxetine combination for the treatment of mixed depression in bipolar I disorder: a post hoc analysis. *The Journal of clinical psychiatry* 2009; **70**(10): 1424-31.
76. Brown EB, McElroy SL, Keck PE, Jr., et al. A 7-week, randomized, double-blind trial of olanzapine/fluoxetine combination versus lamotrigine in the treatment of bipolar I depression. *The Journal of clinical psychiatry* 2006; **67**(7): 1025-33.
77. Brown E, Dunner DL, McElroy SL, et al. Olanzapine/fluoxetine combination vs. lamotrigine in the 6-month treatment of bipolar I depression. *The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum (CINP)* 2009; **12**(6): 773-82.
78. Suppes T, Ketter TA, Gwizdowski IS, et al. First controlled treatment trial of bipolar II hypomania with mixed symptoms: quetiapine versus placebo. *Journal of affective disorders* 2013; **150**(1): 37-43.

79. Vieta E, Suppes T, Eggens I, Persson I, Paulsson B, Brecher M. Efficacy and safety of quetiapine in combination with lithium or divalproex for maintenance of patients with bipolar I disorder (international trial 126). *Journal of affective disorders* 2008; **109**(3): 251-63.
80. Suppes T, Vieta E, Liu S, Brecher M, Paulsson B. Maintenance treatment for patients with bipolar I disorder: results from a north american study of quetiapine in combination with lithium or divalproex (trial 127). *The American journal of psychiatry* 2009; **166**(4): 476-88.
81. Woo YS, Bahk WM, Jon DI, et al. Risperidone in the treatment of mixed state bipolar patients: results from a 24-week, multicenter, open-label study in Korea. *Psychiatry and clinical neurosciences* 2010; **64**(1): 28-37.
82. Bowden CL, Vieta E, Ice KS, Schwartz JH, Wang PP, Versavel M. Ziprasidone plus a mood stabilizer in subjects with bipolar I disorder: a 6-month, randomized, placebo-controlled, double-blind trial. *The Journal of clinical psychiatry* 2010; **71**(2): 130-7.
83. van der Loos ML, Mulder PG, Hartong EG, et al. Efficacy and safety of lamotrigine as add-on treatment to lithium in bipolar depression: a multicenter, double-blind, placebo-controlled trial. *The Journal of clinical psychiatry* 2009; **70**(2): 223-31.
84. Bowden CL, Singh V, Weisler R, et al. Lamotrigine vs. lamotrigine plus divalproex in randomized, placebo-controlled maintenance treatment for bipolar depression. *Acta psychiatrica Scandinavica* 2012; **126**(5): 342-50.